Comparative Pharmacokinetic Assessments of Topical Drugs: Evaluation by Dermatopharmacokinetics, Microdialysis, and Systemic Measurement

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TO THE EDITOR

The conventional pharmacokinetic profiles of drugs are described mainly through the plotting of drug–plasma concentration against time. This is clearly appropriate for most of the orally administered drugs that undergo systemic absorption before distribution to the site of action. However some drugs, such as local anesthetics, antifungal agents, and topical corticosteroids, are designed to target the local tissue where they are applied and, as such, have limited systemic absorption. For these drugs, the pharmacokinetic measurements in the local tissue are of more interest than the systemic measurement. A number of *in vitro* and *in vivo* techniques are available for direct measurement of pharmacokinetic and clinically relevant information about drug concentration in the target tissue and skin. Animal skin and excised human skin are available to use in *in vitro* experiments such as those using Franz-type diffusion cells (Franz, 1976). However, the data obtained from excised skin may not translate directly to the *in vivo* situation. There are a few *in vivo* techniques that enable acquisition of drug concentration information in the skin and a pharmacokinetic profile. These techniques include dermal microdialysis (DMD; Anderson *et al.*, 1992; Hegemann *et al.*, 1995; Benfeldt, 1999), tape stripping or dermatopharmacokinetics (DPK; Pershing *et al.*, 2003), the skin blister fluid method (Nowak and Klimowicz, 1990), magnetic resonance imaging (Jynge *et al.*, 1990), and biopsy followed by tissue homogenization (Roos and Brorson, 1990). Of these techniques, microdialysis and tape stripping are the most widely used for the pharmacokinetic assessment of skin because these methods are easier to perform, produce reliable results, and are less invasive.

In this study, which was approved by the United Kingdom's Central Office for Research Ethics Committees, we evaluated the DMD and tape-stripping (DPK) techniques in the pharmacokinetic assessment of topical drugs and compared the results with those of conventional systemic drug measurements in blood. The study was conducted according to the Declaration of Helsinki Principles. It was an open-label study, with two visits and a 1-week washout period. DMD and blood sampling were performed in parallel on one occasion and DPK was performed on another occasion. The study involved 12 healthy subjects, and participants gave their written informed consent. On the microdialysis study day, a CMA 60 microdialysis catheter was used together with a CMA 106 microdialysis pump supplied by CMA Microdialysis, Solna, Sweden. The adhesive tape used on the DPK study day was TESA 4204 PV5, supplied by TESA, Milton Keyness, UK. EMLA cream (AstraZeneca, Bristol, UK) containing 2.5% lidocaine and 2.5% prilocaine was used as a study drug. In the DMD experiment, the probe (3 cm long) was inserted under the treatment area (subcutaneous tissue) and the sampling was carried out every 20 minutes until 4 hours after the dose. The treatment was 1 g EMLA cream applied to a 10-cm^2 circular area of the skin. A 20-gauge cannula was cannulated on the contralateral arm for the venous sampling. Venous samples were collected at 0, 20, and 40 minutes and 1, 1.5, 2, 2.5, 3, 3.5, and 4 hours after the dose. The residual drug was removed from the treated area 1 hour after treatment application.

On another occasion, the tape stripping was carried out on the skin surface. Tape stripping was performed at 0, 15, 30, and 45 min and 1 hour after the dose for the uptake phase (sites 1, 2, 3, 4, and 5) and 1.5, 2, 3, and 4 hours after the dose for the elimination phase (sites 6, 7, 8, and 9). The treatments were 1 g EMLA cream applied to 10 demarcated rectangular areas of the skin (6 cm^2). Before collection of stratum corneum from the treated skin site, the residual product was removed from the skin surface using a metal spatula and three dry cotton-wool tips used independently. Site 1 served as a control (0 hour sampling). The residual product was removed at 15, 30, and 45 min from sites 2, 3, and 4. For sites 5–9, the residual product was removed at 1 hour. After product removal from the skin, the first adhesive tape was applied and briskly rubbed with blunt-ended forceps to collect the stratum corneum. The tape was removed using the forceps. As a precaution, the first adhesive tape was discarded to avoid potential contamination from any residual product not removed with the dry cotton wool (Weigmann *et al.*, 1999). The remaining nine adhesive tapes were applied sequentially using the procedure described above and kept in a polypropylene tube until further analysis. The lidocaine concentration from plasma and DMD samples was

Abbreviations: DMD, dermal microdialysis; DPK, dermatopharmacokinetic

Table 1. Pharmacokinetic parameters (mean AUC_{0-4}, C_{max} (0–4), $t_{1/2}$, and median t_{max}) obtained with three methods after application of EMLA cream in 12 healthy subjects

PK parameter	DPK	DMD	Plasma
AUC_{0-4}	712.3 μg h^{-1}	458 ng ml^{-1} h^{-1}	4.1 ng ml^{-1} h^{-1}
C_{max} (0–4)	320.8 μg	426 ng ml^{-1}	2.5 ng ml^{-1}
t_{max} (h)	1.0	NA	3.25
$t_{1/2}$ (h)	2.5	NA	1.9
CV for AUC (%)	36	148	49
CV for (C_{max}) (%)	26	134	75

Abbreviations: AUC, area under the curve; CV, coefficient of variation; DMD, dermal microdialysis; DPK, dermatopharmacokinetics; NA, not available.

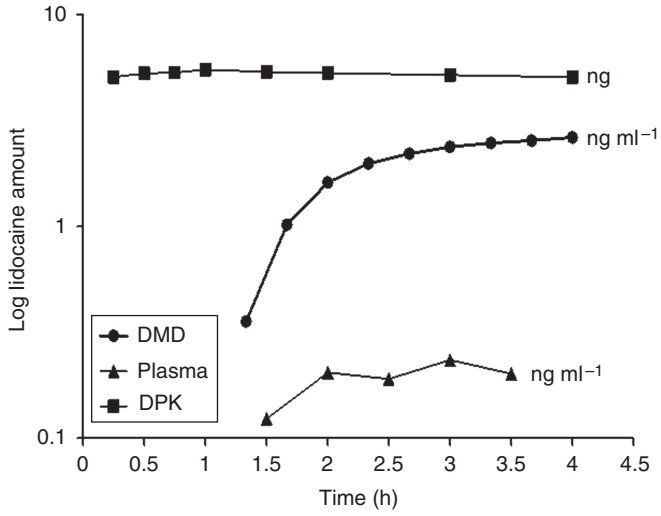

Figure 1. Plot of mean lidocaine concentration versus time (h) in tape, dialysate, and plasma samples on log scales.

analyzed using the validated liquid chromatography–mass spectrometry/mass spectrometry method (Chik *et al.*, 2006), and the lidocaine content in the tape samples was analyzed using capillary electrophoresis with UV detection (Chik *et al.*, 2007).

Table 1 summarizes the pharmacokinetic parameters derived for lidocaine, and Figure 1 shows the lidocaine concentration-versus-time plot for all the three methods studied. There was a higher area under the curve and C_{max} (maximum plasma concentration) with DPK as compared with DMD and plasma. The median time to the highest plasma lidocaine concentration, t_{max}, was significantly shorter in the stratum corneum as compared with plasma, with values of 1.00 versus 3.25 hours ($P<0.001$). The higher lidocaine profile yielded by the DPK and DMD methods is advantageous for pharmacokinetic measurement when compared with the low lidocaine profiles obtained from systemic measurement. The results showed that lidocaine was rapidly detected in the stratum corneum soon after treatment application. At 1 hour after application of EMLA, its levels in the stratum corneum were higher than those in the subcutaneous layer of the skin or in blood. The decrease in the amount of lidocaine after 1 hour in the DPK samples can be explained by the increased of lidocaine concentration in the dialysate. This remained elevated even at the 4-hour sampling time. In a comparison of the DPK and DMD methods, good reproducibility and less variability were shown by the DPK method. The greater variability in the DMD data than with plasma and DPK may be a reflection of the depth of the probe implantation, as the same subjects were used for all three techniques. Moreover, the validation of within- and between-probe recovery showed a low variability in the three probes studied. Therefore, between- and within-probe variability was minimal and did not contribute significantly to the variability observed. However, more research and data regarding the reliability of DMD and DPK are necessary to determine the ideal methods for pharmacokinetic assessment of topical drugs.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Quality of Life in Alopecia Areata: A Study of 60 Cases

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TO THE EDITOR

Alopecia areata (AA) is a chronically relapsing skin disorder characterized by a sudden loss of hair. Because the perception of patients may differ significantly from those of their health-care providers, quality of life (Qol) appears to be a more relevant criterion to assess the severity of this disease than clinical evaluation such as AA extension. To our knowledge, only one Turkish study investigated the impact of AA on Qol using short form 36 (SF36), indicating lower Qol levels compared with sex-matched individuals (Gulec *et al.*, 2004). In this study, Qol was assessed using a generic instrument. Because only three dimensions were affected and results may be linked to the specific culture, a confirmation was needed. We used an approach combining generic and specific measures to assess the impact of AA on French patients' Qol, to compare Qol levels with those observed in the general population and in other dermatological conditions, and finally to determine the impact of clinical characteristics and sociodemographic factors on Qol.

Subjects were aged over 16 years, presenting with a minimum of 8 weeks AA history, having given informed consent to participate, and having the French language as their native language. Sociodemographic data and characteristics of the disease (duration and course, treatments in the recent period, affected surfaces on the scalp and other areas involved) were recorded. The severity of each AA was reported using visual analogical scales (0–10) by reference to (i) all the AA cases seen in daily practice; (ii) all cases of all skin disorders. Three self-administered questionnaires were used to assess Qol: the generic and worldwide-used SF36 (Leplege *et al.*, 1998, 2001; Coste, 2001), and two ''chronic skin disorders''-specific Qol instruments with French validated available versions, the VQ-Dermato (Grob *et al.*, 1999, 2009) and the Skindex (Chren *et al.*, 1996, 1997; Leplege *et al.*, 2003). To better figure out the level of QoL in AA, we compared AA scores with those available in literature related to the French population: (1) rare dermatological diseases including hidradenitis suppurativa (Wolkenstein *et al.*, 2007) and neurofibromatosis type 1 (Wolkenstein *et al.*, 2001); (2) chronic/frequent dermatological diseases including psoriasis, chronic idiopathic urticaria, and atopic dermatitis (Grob *et al.*, 2005); (3) general population: French age- and sex-matched controls (Leplege *et al.*, 2001). This study was conducted in adherence to the Helsinki guidelines. Institutional approval was not required for experiments. After having given their inform consent, 60 patients were included (39 women and 21 men); their mean age was 40.1 years (SD 15.2) and median AA duration was 6 years (2 months to 60 years). Course of the disease was stable in 25 subjects and unstable in 35. The median of the scalp surface involved was 77%. The median of severity score was 6.5 (range 4.0–9.0) by reference to the AA patients and 3.5 (range 2.0–6.0) by reference to the patients presenting any skin disorder.

Mental health and vitality were the most altered SF36 dimensions, whereas physical functioning, role physical and body pain were the least ones. Regarding VQ-Dermato, daily life, leisure activity, and physical discomfort were the least altered dimensions. For Skindex, emotions dimension was the most affected and symptoms the least one. Compared with the general population and with patients suffering from other dermatological conditions (Table 1), AA patients presented significantly altered Qol for almost all the SF36 dimensions. For VQ-Dermato, AA patients reported (i) significantly better (mood state, leisure activity, daily life, and physical discomfort) or worse scores (self-perception) than psoriasis, chronic idiopathic urticaria, and atopic dermatitis patients; (ii) being less bothered to treatment-induced restrictions than psoriasis, but more than chronic idio-

Abbreviations: AA, alopecia areata; Qol, quality of life; SF36, short form 36